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(54) Title: RETRO-ANANDAMIDES, HIGH AFFINITY AND STABILITY CANNABINOID RECEPTOR LIGANDS

(57) Abstract: Novel retro-anandamides are presented which have high affinities for the cannabinoid CB1 and/or CB2 receptor sites. Further, most of the analogs exhibit greater metabolic stability than arachidonylethanolamide. The improved receptor affinity and selectivity and/or greater metabolic stability make these analogs therapeutically useful as medications in individuals and animals for treatment of pain, glaucoma, epilepsy, nausea associated with chemotherapy, as well as suppression of the immune system, enhancement of appetite and in treatment of certain mental disorders.

RETRO-ANANDAMIDES, HIGH AFFINITY AND STABILITY CANNABINOID RECEPTOR LIGANDS

Field of the Invention

5 The present invention relates generally to cannabinoid analogs and is more particularly concerned with new and improved retro-anandamide cannabinoid analogs exhibiting high binding affinities for cannabinoid receptors, pharmaceutical preparations employing these analogs and methods of administering therapeutically effective amounts of the preparations to provide a
10 physiological effect.

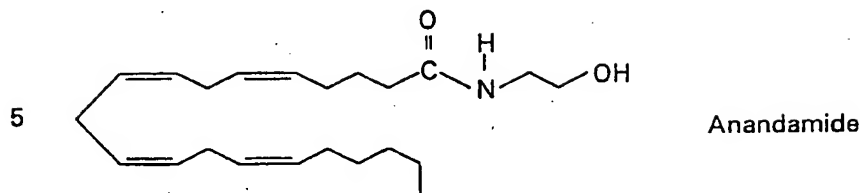
Background of the Invention

Classical cannabinoids such as the marijuana derived cannabinoid Δ^9 -tetrahydrocannabinol, (Δ^9 -THC) produce their pharmacological effects through
15 interaction with specific cannabinoid receptors in the body. So far, two cannabinoid receptors have been characterized: CB1, a central receptor found in the mammalian brain and peripheral tissues and CB2, a peripheral receptor found only in the peripheral tissues. Compounds that are agonists or antagonists for one or both of these receptors have been shown to provide a variety of
20 pharmacological effects. See, for example, Pertwee, R.G., Pharmacology of cannabinoid CB1 and CB2 receptors, Pharmacol. Ther., (1997) 74:129 - 180 and Di Marzo, V., Melck, D., Bisogno, T., DePetrocellis, L., Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action, Trends Neurosci. (1998) 21:521 - 528.

25 In addition to acting at the cannabinoid receptors, cannabinoids such as Δ^9 -THC also affect cellular membranes, thereby producing undesirable side effects such as drowsiness, impairment of monoamine oxidase function and impairment of non-receptor mediated brain function. The addictive and psychotropic properties of some cannabinoids also limit their therapeutic value.

30 Arachidonylethanolamide (anandamide) is an endogenous lipid that binds to and activates the CB1 cannabinoid receptor with approximately

equal affinity to that of Δ^9 -THC.



Anandamide also exhibits biochemical and pharmacological properties similar to that of Δ^9 -THC, albeit with a longer onset time and shorter duration of action.

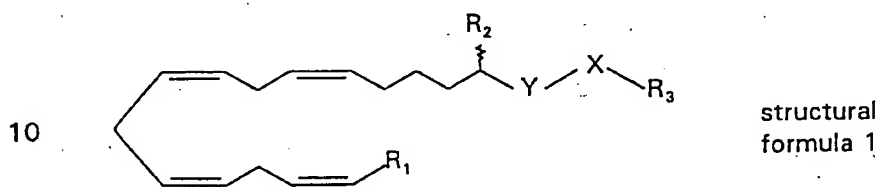
- 10 The exact physiological role of anandamide, a cannabinoid agonist, is still not clearly understood. It is known that an enzyme called "anandamide amidase" hydrolyzes anandamide. It is presumed that the magnitude of action and relatively short duration of action of anandamide is due to a rapid inactivation process consisting of carrier-mediated transport into cells followed by intra-
- 15 cellular hydrolysis by anandamide amidase.

- Presently known anandamide analogues show susceptibility towards enzymatic hydrolysis and/or have low receptor affinity. There is considerable interest in developing analogs of anandamide possessing high CB1 receptor affinity and/or metabolic stability. Such analogs may offer a rational therapeutic
- 20 approach to a variety of disease states in which elevation of anandamide analog levels may bring about a more favorable response with fewer side effects and greater metabolic stability than direct activation of CB1 receptors by anandamide.

25 Summary of the Invention

- It has now been found that certain novel analogs of anandamide and physiologically acceptable salts thereof possess improved CB1 receptor affinity and selectivity and/or greater metabolic stability than anandamide. The term "metabolic stability" as used herein refers to the resistance to hydrolysis of the
- 30 subject anandamide analog by anandamide amidase. Thus, the novel analogues described herein should have a longer duration of action than anandamide.

Thus one aspect of the invention are the analogs of anandamide generally shown in structural formula 1. The novel analogs were prepared by structural modification of anandamide. The modifications were primarily made in the ethanolamido head group and included reversing the positions of the NH and CO groups. Such anandamide analogues wherein the NH and CO group positions are reversed are known as "retro-anandamides".



wherein:

X is selected from the group consisting of C=O, and C=S;

15 Y is NH;

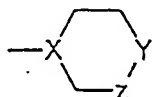
R₁ is selected from the group consisting of n-C₅H₁₀Z, n-C₈H₁₂Z, n-C₇H₁₄Z, and 1'1'-C(CH₃)₂(CH₂)₅CH₂Z, wherein Z is selected from the group consisting of H, halogen, N₃, NCS, OH, CN and -CH=CH-I;

R₂ is selected from the group consisting of H, CH₃, and (CH₃)₂; and

20 R₃ is selected from the group consisting of CH₃, CHX₂, CH₂X, CH=CH₂, CH₂OCH₃, -C≡CH, -O(CH₂)_nCH₃, -S(CH₂)_nCH₃, $\begin{matrix} \text{---N---(CH}_2\text{)}_n\text{CH}_3 \\ | \\ \text{(CH}_2\text{)}_m\text{CH}_3 \end{matrix}$

wherein n and m are each a number from 0 to about 7,

25

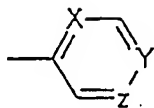


wherein X is selected from the group consisting of

N and CH and Y and Z are each selected from the group consisting of (CH₂)_n, O, N, and S, and

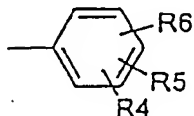
wherein n is a number from 0 to about 7,

30



wherein X, Y and Z are each selected from the group consisting of CH and N,

5



wherein R4, R5 and R6 are each selected from the group consisting of halogen, N₃, NCS, OCH₃, CH₃, CH₂CH₃, NO₂, NH₂ and phenyl.

In another aspect of the invention, increased metabolic stability and resistance to enzymatic hydrolysis are achieved by introducing steric bulk in the form of alkyl groups around the amide bond or suitable modification of the amide bond itself.

The inventive anandamide analogues of this invention are metabolically stable (i.e., have low or no enzyme turnover) and show significantly higher cannabinoid receptor affinities and selectivities. The improved receptor affinity and selectivity and/or metabolic stability create therapeutic uses for the novel analogs. Therefore, the novel compounds described herein, and physiologically acceptable salts thereof, represent potentially useful materials for providing a physiological effect to treat The inventive analogs described herein, and physiologically acceptable salts thereof, have high potential when administered in therapeutically effective amounts for providing a physiological effect useful to treat pain; peripheral pain; glaucoma; epilepsy; nausea such as associated with cancer chemotherapy; AIDS Wasting Syndrome; cancer; neurodegenerative diseases including Multiple Sclerosis, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease; to enhance appetite; to reduce fertility; to prevent or reduce diseases associated with motor function such as Tourette's syndrome; to provide neuroprotection; to produce peripheral vasodilation and to suppress memory. Thus, another aspect of the invention is the administration of a therapeutically effective amount of an inventive compound, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological effect.

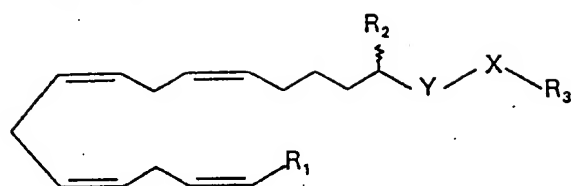
Description of Some Preferred Embodiments

As used herein a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to
5 cause a discernible increase or decrease in stimulation of cannabinoid receptors. Physiological effects which result from cannabinoid receptor stimulation include analgesia, decreased nausea resulting from chemotherapy, sedation and increased appetite. Other physiological functions include relieving intraocular pressure in glaucoma patients and suppression of the immune system. Typically,
10 a "therapeutically effective amount" of the compound ranges from about 10 mg/day to about 1,000 mg/day.

As used herein, an "individual" refers to a human. An "animal" refers to, for example, veterinary animals, such as dogs, cats, horses and the like, and farm animals, such as cows, pigs and the like.

15 The compound of the present invention can be administered by a variety of known methods, including orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to, capsular and tablet
20 formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular or subcutaneous administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically to
25 acceptable vehicles may include, for example, saline, sterile water, Ringer's solution, and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

30 The inventive retro-anandamides can generally be described with reference to structural formula 1 includes physiologically acceptable salts thereof.

structural
formula 1

5

wherein:

X is selected from the group consisting of $C=O$, and $C=S$;

Y is NH;

10

R_1 is selected from the group consisting of $n-C_5H_{10}Z$, $n-C_6H_{12}Z$, $n-C_7H_{14}Z$, and $1'1'-C(CH_3)_2(CH_2)_5CH_2Z$, wherein Z is selected from the group consisting of H, halogen, N_3 , NCS, OH, CN and $-CH=CH-I$;

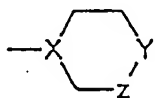
 R_2 is selected from the group consisting of H, CH_3 , and $(CH_3)_2$; and

15

R_3 is selected from the group consisting of CH_3 , CHX_2 , CH_2X , $CH=CH_2$, CH_2OCH_3 , $-C\equiv CH$, $-O(CH_2)_nCH_3$, $-S(CH_2)_nCH_3$, $-N-(CH_2)_nCH_3$, $(CH_2)_mCH_3$

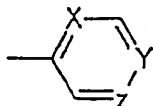
wherein n and m are each a number from 0 to about 7,

20



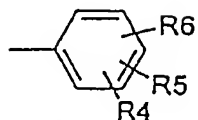
wherein X is selected from the group consisting of N and CH and Y and Z are each selected from the group consisting of $(CH_2)_n$, O, N, and S, and wherein n is a number from 0 to about 7,

25



wherein X, Y, and Z are each selected from the group consisting of CH and N,

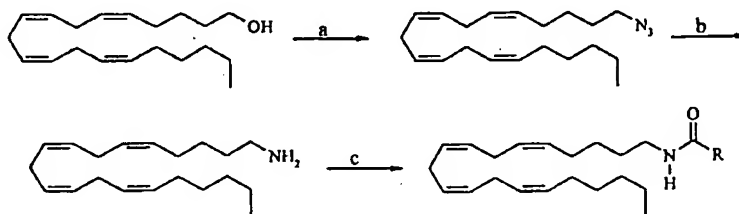
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wherein R4, R5 and R6 are each selected from the group consisting of halogen, N₃, NCS, OCH₃, CH₃, CH₂CH₃, NO₂, NH₂ and phenyl.

- 5 The novel retro-anandamide analogs possess high metabolic stability and/or high CB1 receptor affinity and selectivity. The high CB1 receptor affinity and selectivity functions to make these analogs useful for the treatment of at least the previously described conditions when administered to an individual or animal in a therapeutically effective amount without the unwanted side effects
- 10 that are a result of use of known cannabinoids to stimulate the CB1 and CB2 receptors. Additionally, the high metabolic stability of the novel analogs function to provide a longer lasting effect than is typical of known cannabinoids.

The inventive materials were generally prepared according to scheme 1 below:



15

(a) ZnN₆Py, Ph₃P, DIAP, toluene; (b) LiAlH₄, diethyl ether; (c) Et₃N, DMF, acid chloride.

General. Column chromatography was carried out using Selecto Scientific active silica gel (230 - 400 mesh), and eluents were distilled before use.

- 20 Solvents for reactions were dried or purified as required. Reactions were carried out under argon atmospheres unless otherwise noted. Arachidonyl alcohol was purchased from Nu-Chek-Prep, Inc., Elysian, Mn. Rat brains were purchased from Pelfreeze Rogers, Ar.

- 25 Arachidonyl azide. To a magnetically stirred solution of 3.6 g (13.7 mmol) of Ph₃P in 30 mL anhydrous toluene was added 2.0 g (6.9 mmol) of arachidonyl alcohol. Then 1.6 g (5.2 mmol) of ZnN₆•Py was added into the reaction mixture.

To this stirred mixture at room temperature, 2.7 mL (13.7 mmol) of diisopropyl azodicarboxylate was added dropwise, causing a slightly exothermal reaction.

Stirring was continued until complete consumption (TLC monitoring) of alcohol (<2hours) was observed. The heterogeneous mixture was filtered over a celite
5 pad, concentrated in *vacuo* and purified by column chromatography on silica gel with petroleum ether/dichloromethane (5:1) to give 2.0 g (92%) of arachidonyl azide as a colorless oil.

Arachidonyl amine. To a magnetically stirred solution of 2.0 g (6.3 mmol)
10 of arachidonyl azide in 40 mL of dry diethyl ether was added 10 mL of a 1.0 M solution of lithium aluminum hydride (10 mmol) in THF dropwise at room temperature. The reaction mixture was refluxed for 3hours (h) and then quenched with wet diethyl ether. The white suspension was filtered, and the filtrate was evaporated to dryness. Chromatography on silica gel (10-50%
15 MeOH in dichloromethane) gave 1.8 g (98%) as a colorless oil.

General procedure for the preparation of retro-anandamides. To a magnetically stirred solution of 0.55 mmol arachidonyl amine and 0.1 mL (0.72 mmol) of triethylamine in 4 mL of anhydrous dichloromethane was added 0.84
20 mmol of acid chloride in 1 mL dichloromethane. After stirring at room temperature for 3 h, the reaction mixture was added with brine and extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Column chromatography on silica gel with ethyl acetate/petroleum ether gave retro-
25 anandamides as oil.

A person of ordinary skill in the art, understanding the disclosures for the general preparation and specific preparation examples would know how to modify the disclosed procedures to achieve the above listed analogs.

The materials were tested for CB2 receptor binding affinity and for CB1
30 receptor affinity (to determine selectivity for the CB2 receptor). As used herein, "binding affinity" is represented by the IC_{50} value which is the concentration of

an analog required to occupy 50% of the total number (B_{max}) of the receptors.

The lower the IC_{50} value the higher the binding affinity. As used herein an analog is said to have "binding selectivity" if it has higher binding affinity for one receptor compared to the other receptor; e.g. a cannabinoid analog which has an
5 IC_{50} of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor. The binding affinities (K_i) are expressed in nanomoles (nM) and are listed in TABLE 1.

It is known that the enzymatic action of anandamide amidase can be moderated or prevented in vitro by the inclusion of phenylmethanesulfonyl
10 fluoride (PMSF). PMSF functions as a non-selective protease inhibitor. Thus the ligand binding determinations for the CB1 receptor were carried out twice, once in the presence and once in the absence of PMSF, to obtain both CB1 receptor binding affinity and a relative measure of the analog's metabolic stability. The binding affinities (K_i) are expressed in nanomoles (nM).

15 For the CB1 receptor binding studies, membranes were prepared from rat forebrain membranes according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W.A. Devane et al,
20 Determination and Characterization of a Cannabinoid Receptor in a Rat Brain, Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al, 5'-azido Δ^8 -THC: A Novel Photoaffinity Label for the Cannabinoid Receptor, J. Med. Chem., 35, 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

25 Membranes, previously frozen at -80°C , were thawed on ice. To the stirred suspension was added three volumes of TME (25mM Tris-HCl buffer, 5 mM MgCl_2 and 1 mM EDTA) at a pH 7.4 containing 150 μM PMSF (made fresh in 2-propanol as a 100 mM stock). The suspension was incubated at 4°C , and after 15 min a second addition of PMSF stock brought the concentration to 300
30 μM PMSF; then the mixture was incubated for another 15 min. At the end of

the second 15-min incubation, the membranes were pelleted and washed three times with TME to remove unreacted PMSF.

The treated membranes were subsequently used in the binding assay described below. Approximately 30 μ g of PMSF-treated membranes were incubated in silanized 96-well microtiter plate with TME containing 0.1% essentially fatty acid-free bovine serum albumin (BSA), 0.8 nM [3 H] CP-55,940, and various concentrations of anandamide analogues at 30 °C for 1 hour. The samples were filtered using Packard Filtermate 196 and Whatman GF/C filterplates and washed with wash buffer (TME containing 0.5% BSA).

10 Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with duplicate determinations was normalized between 100% and 0% specific binding

15 for [3 H] CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4-parameter nonlinear logistic equation to yield IC_{50} values. Data from at least two independent experiments performed in duplicate was used to calculate IC_{50} values which were converted to K_i values using the using the assumptions of Cheng et al, Relationship Between the

20 Inhibition Constant (K_i) and the concentration of Inhibitor which causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction, Biochem. Pharmacol., 22, 3099-3102, (1973), which is incorporated by reference herein.

The CB1 ligand binding determinations in the absence of PMSF were performed in a similar manner to the above test, except without the use of

25 PMSF.

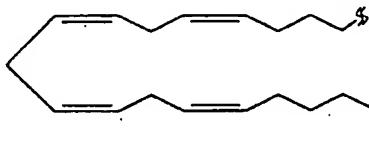
For the CB2 receptor binding studies, membranes were prepared from frozen mouse spleen essentially according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 226, 107 - 118 (1981). Silanized centrifuge tubes were

30 used throughout to minimize receptor loss due to adsorption. The CB2 binding assay was conducted in the same manner as for the CB1 binding assay except

the assays were conducted without PMSF. Since the CB2 receptor preparation has been shown to be devoid of anandamide amidase, the presence or absence of PMSF was not considered to be determinative. The binding affinities (K_i) are expressed in nanomoles (nM).

- 5 The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the practice of the invention. As used herein, AA refers to that portion of the anandamide molecule having the structure:

10



Examples of the following specific analogs were prepared and tested according to the procedures and protocols discussed above.

15

TABLE 1

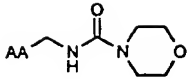
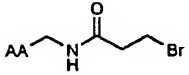
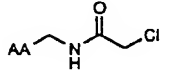
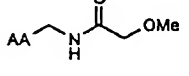
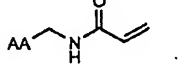
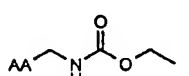
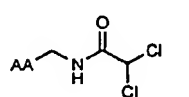
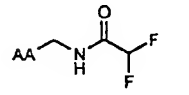
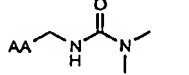
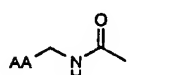
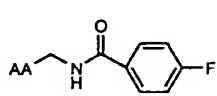
5	1		<i>N</i> -(4-Morpholinecarbonyl) arachidonylamine
	2		<i>N</i> -(3-Bromopropionyl) arachidonylamine
10	3		<i>N</i> -(2-Chloroacetyl) arachidonylamine
	4		<i>N</i> -(2-Methoxyacetyl) arachidonylamine
15	5		<i>N</i> -Acryloyl arachidonylamine
	6		Arachidonylcarbamic acid ethyl ester
20	7		<i>N</i> -(2-Dichloroacetyl) arachidonylamine
25	8		<i>N</i> -(2-Difluoroacetyl) arachidonylamine
	9		<i>N</i> -Dimethylcarbamyl arachidonylamine
30	10		<i>N</i> -Acetyl arachidonylamine
35	11		<i>N</i> -(4-Fluorobenzoyl) arachidonylamine

TABLE 2			
analog	K _i (CB1) nM		K _i (CB2) nM
	with PMSF	without PMSF	
1	23.9	35.4	100.3
2	17.4	70.6	very high
3	3.33	4.39	91.4
4	2.08	4.22	89.8
5	9.06	47.8	330
6	162.2	249.1	653.9
7	0.01	0.001	21.2
8	0.06	0.11	304.8
9	4.09	1.18	178.3
10	1.56	1.71	5320
11	180.7	174	386

Experimental preclinical data using a discriminating behavior test shows at least one of the analogs is 20 to 50 times more potent than the endogenous cannabinoid ligand, anandamide.

The physiological and therapeutic advantages of the inventive materials can be seen with additional reference to the following references, the disclosures of which are hereby incorporated by reference. Arnone M., Maruani J., Chaperon P, *et al*, Selective inhibition of sucrose and ethanol intake by SR141716, an antagonist of central cannabinoid (CB1) receptors, Psychopharmacol, (1997) 132, 104-106. Colombo G, Agabio R, Diaz G. et al: Appetite suppression and weight loss after the cannabinoid antagonist SR141716. Life Sci. (1998) 63-PL13-PL117. Simiand J, Keane M, Keane PE, Soubrie P: SR 141716, A CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset. Behav. Pharmacol (1998) 9:179-181. Brotchie JM: Adjuncts to dopamine replacement a pragmatic approach to reducing the problem of dyskinesia in Parkinson's disease. Mov. Disord. (1998).

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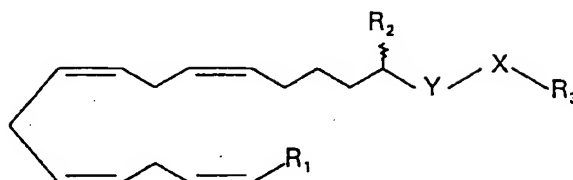
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The inventive analogs described herein, and physiologically acceptable 15 salts thereof, have high potential when administered in therapeutically effective amounts for providing a physiological effect useful to treat pain; peripheral pain; glaucoma; epilepsy; nausea such as associated with cancer chemotherapy; AIDS Wasting Syndrome; cancer; neurodegenerative diseases including Multiple Sclerosis, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease; to 20 enhance appetite; to reduce fertility; to prevent or reduce diseases associated with motor function such as Tourette's syndrome; to provide neuroprotection; to produce peripheral vasodilation and to suppress memory. Thus, another aspect of the invention is the administration of a therapeutically effective amount of an inventive compound, or a physiologically acceptable salt thereof, to an individual 25 or animal to provide a physiological effect.

Those skilled in the art will recognize, or be able to ascertain with no more than routine experimentation, many equivalents to the specific embodiments of the invention disclosed herein. Such equivalents are intended to be encompassed by the scope of the invention.

What Is Claimed Is:

1. A compound of the formula :



wherein:

X is selected from the group consisting of C = O, and C = S;

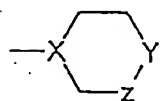
Y is NH;

R₁ is selected from the group consisting of n-C₅H₁₀Z, n-C₆H₁₂Z, n-C₇H₁₄Z, and 1'1'-C(CH₃)₂(CH₂)₅CH₂Z, wherein Z is selected from the group consisting of H, halogen, N₃, NCS, OH, CN and -CH=CH-I;

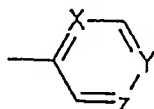
R₂ is selected from the group consisting of H, CH₃, and (CH₃)₂; and

R₃ is selected from the group consisting of CH₃, CHX₂, CH₂X, CH=CH₂, CH₂OCH₃, -C≡CH, -O(CH₂)_nCH₃, -S(CH₂)_nCH₃, $\begin{array}{c} \text{---N---(CH}_2\text{)}_n\text{CH}_3 \\ | \\ \text{(CH}_2\text{)}_m\text{CH}_3 \end{array}$

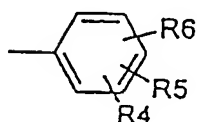
wherein n and m are each a number from 0 to about 7,



wherein X is selected from the group consisting of N and CH and Y and Z are each selected from the group consisting of (CH₂)_n, O, N, and S, and wherein n is a number from 0 to about 7,

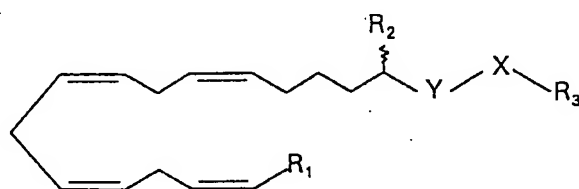


wherein X, Y and Z are each selected from the group consisting of CH and N,



wherein R₄, R₅ and R₆ are each selected from the group consisting of halogen, N₃, NCS, OCH₃, CH₃, CH₂CH₃, NO₂, NH₂ and phenyl.

2. The compound of claim 1 wherein X is C=O.
3. A method of preferentially stimulating the CB1 receptors in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound having the formula:



wherein:

X is selected from the group consisting of C=O, and C=S;

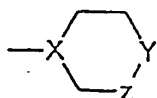
Y is NH;

R₁ is selected from the group consisting of n-C₅H₁₀Z, n-C₆H₁₂Z, n-C₇H₁₄Z, and 1'1'-C(CH₃)₂(CH₂)₅CH₂Z, wherein Z is selected from the group consisting of H, halogen, N₃, NCS, OH, CN and -CH=CH-I;

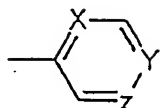
R₂ is selected from the group consisting of H, CH₃, and (CH₃)₂; and

R₃ is selected from the group consisting of CH₃, CHX₂, CH₂X, CH=CH₂, CH₂OCH₃, -C≡CH, -O(CH₂)_nCH₃, -S(CH₂)_nCH₃, $\begin{array}{c} \text{---N---(CH}_2\text{)}_n\text{CH}_3 \\ | \\ \text{(CH}_2\text{)}_m\text{CH}_3 \end{array}$

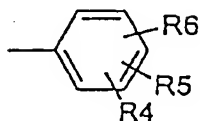
wherein n and m are each a number from 0 to about 7,



wherein X is selected from the group consisting of N and CH and Y and Z are each selected from the group consisting of (CH₂)_n, O, N, and S, and wherein n is a number from 0 to about 7,



wherein X, Y and Z are each selected from the group consisting of CH and N,



wherein R4, R5 and R6 are each selected from the group consisting of halogen, N₃, NCS, OCH₃, CH₃, CH₂CH₃, NO₂, NH₂ and phenyl.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

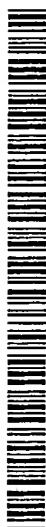
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- (21) International Application Number: PCT/US00/41248 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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- (71) Applicant (*for all designated States except US*): UNIVERSITY OF CONNECTICUT [US/US]; 263 Farmington Avenue, Farmington, CT 06032 (US).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 01/28498 A3

(54) Title: RETRO-ANANDAMIDES, HIGH AFFINITY AND STABILITY CANNABINOID RECEPTOR LIGANDS

(57) Abstract: Novel retro-anandamides are presented which have high affinities for the cannabinoid CB1 and/or CB2 receptor sites. Further, most of the analogs exhibit greater metabolic stability than arachidonylethanolamide. The improved receptor affinity and selectivity and/or greater metabolic stability make these analogs therapeutically useful as medications in individuals and animals for treatment of pain, glaucoma, epilepsy, nausea associated with chemotherapy, as well as suppression of the immune system, enhancement of appetite and in treatment of certain mental disorders.

INTERNATIONAL SEARCH REPORT

International application No.
PCT US00-41248

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 233-00; A01N 37 18

US Cl. : 564-192; 564 204; 514-613

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564-192; 564 204; 514 613

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
caplus, east, caold

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,874,459 A (MAKRIYANNIS et al.) 23 February 1999, see the entire document	1 and 2
Y	US 5,688,825 A (MAKRIYANNIS et al.) 18 November 1997, see the entire document.	1 and 2
Y	US 4,812,457 A (NARUMIYA et al.) 14 March 1989, see the entire document.	Claims 1 and 2
A	US 5,925,628 A (LEE et al.) 20 July 1999, see the entire document.	1-3
Y	US 5,618,955 A (MECHOULAM et al) 08 April 1997, see the entire document.	1 and 2



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents	* T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* N* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

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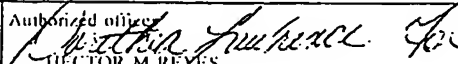
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